II. Remarks

Claims 32, 38-40 and 42-68 are pending in this application. Claims 60-68 were previously withdrawn from further consideration. Claims 1-6, 8-31, 33-37 and 41 were previously cancelled. Claims 32, 50 and 57 are amended. Upon entry of these amendments, claims 32, 38-40 and 42-68 are pending with claims 32, 38-40 and 42-59 being under active consideration. Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application.

Claim 32 is amended to limit the reference sequence to nucleotides 328 to 2751 of SEQ ID NO: 1, support for which may be found at page 109, line 11. Claim 32 is also amended to change "detecting" to "measuring," support or which may be found at page 4, lines 4-8. Claim 32 is also amended to add "colorectal," support for which may be found at page 4, lines 9-10.

Claim 50 is amended to limit the reference sequence to nucleotides 328 to 2751 of SEQ ID NO: 1, support for which may be found at page 109, line 11. Claim 50 is also amended to change "detecting" to "measuring," support or which may be found at page 4, lines 4-8. Claim 50 is also amended to add "colorectal," support for which may be found at page 4, lines 9-10.

Claim 57 is amended to recite the phrase "wherein an increase in the level of the expression product relative to normal colorectal tissue is indicative of colorectal cancer," support for which may be found at page 11, lines 11-13.

A. Patentability Arguments

1. 35 U.S.C. § 101

a. Lack Of Specific And Substantial Asserted Utility Or A Well-Established Utility

At section 8 of the Final Office Action, the Examiner maintains the rejection of claims 32, 38-40 and 42-59 under 35 U.S.C. § 101 on the grounds that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. The Examiner asserts that the specification does not teach whether the gene encoding the CBF9 polypeptide of SEQ ID NO:2 is over- or under-expressed in colorectal cancer cells. Applicant respectfully disagree.

Table 1 lists genes that were found to be overexpressed in colorectal cancer cells. Applicants note that the Applicants' internal reference number "W07459" associated with the gene encoding the polypeptide of SEQ ID NO:2 may be found as the seventh entry listed on Table 1. *See* page 69, line 10. In view of the accession number associated with the CBF9 gene being set forth on Table 1, Applicants respectfully submit that the disclosure makes it readily apparent to one of ordinary skill in the art that differential expression of CBF9 may be used as a diagnostic for colorectal cancer. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 101 be reconsidered and withdrawn.

b. Genbank Accession Number AC005383

At section 8 of the Final Office Action, the Examiner notes that Table 2 at page 109 of the application discloses the polynucleotide sequence of SEQ ID NO: 1 and also lists Genbank accession number AC005383. As noted by the Examiner at section 12 of the Office Action mailed February 26, 2004, SEQ ID NO: 1 is 3,375 nucleotides in length whereas AC005383 is 1,217,714 nucleotides in length. At section 9 of the outstanding Office Action, the Examiner requested clarification regarding the apparent discrepancy in length of the polynucleotides. Applicants respectfully point out to the Examiner that the polynucleotide sequence of SEQ ID NO: 1 is found within the sequence of AC005383. For the convenience of the Examiner, Applicants attach herewith at Appendix A the results of a BLAST search which indicates the alignment of SEQ ID NO: 1 to AC005383.

2. 35 U.S.C. § 112, first paragraph

a. Lack Of Specific And Substantial Asserted Utility Or A Well-Established Utility - Lack of Enablement

At section 9 of the Final Office Action, the Examiner maintains the rejection of claims 32, 38-40 and 42-59 under 35 U.S.C. § 112, first paragraph on the grounds that the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above in the rejection under 35 U.S.C. § 101. Applicants respectfully disagree. Applicants respectfully submit that, for the reasons provided in section 1 above, claims 32, 38-40 and 42-59 have utility, and thus that one of ordinary skill in the art would have sufficient disclosure to make and use the claimed methods.

b. Lack Of Enablement

At section 10 of the Final Office Action, the Examiner maintains the rejection of claims 32, 38-40 and 42-59 under 35 U.S.C. § 112, first paragraph on the grounds that the claimed

invention is not enabled by the specification. The Examiner alleges that the skilled artisan could not use the claimed invention without the need to perform an undue amount of additional experimentation to determine if variants of the gene encoding the polypeptide of SEQ ID NO:2 are associated with colorectal cancer. Applicants respectfully disagree.

The test of enablement is not whether experimentation is necessary, but whether, if experimentation is necessary, it is undue. *See* MPEP § 2164.01. Moreover, The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See* MPEP § 2164.01.

All that is required for the skilled artisan to practice the full scope of the invention is that a potential variant of a gene encoding the polypeptide of SEQ ID NO:2 be tested for altered expression in a colorectal tumor compared to normal tissue. Applicants respectfully submit that such experimentation is typical and is certainly not undue. As evidence of routine experimentation using methodologies available to those of ordinary skill in the art, Applicants point to Example 1, which discloses the testing and positive identification of thousands of genes associated with colorectal cancer based on altered expression. In view of the numerous working examples provided in the disclosure and the availability of testing methodologies, the disclosure is enabling for practicing the claimed methods. Accordingly, Applicants respectfully request that the rejection for lack of enablement be reconsidered and withdrawn.

c. Lack Of Written Description

At section 11 of the Final Office Action, the Examiner maintains the rejection of claims 32, 38-40 and 42-56 under 35 U.S.C. § 112, first paragraph on the grounds that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner once again relies on Skolnick et al. (2000) ("Skolnick") to assert that the art is unpredictable with respect to a polynucleotide that is 90% identical to SEQ ID NO:1, as a whole. Applicants respectfully traverse the rejection. Applicants respectfully submit that the Examiner has mischaracterized the teachings of Skolnick, and in doing so, has mischaracterized the predictability of the art. Applicants respectfully submit that the amended claims, taking into account the proper characterization of the teachings of Skolnick, satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

As a preliminary matter, Applicants note that claim 32 is amended to limit the reference sequence to nucleotides 328 to 2751 of SEQ ID NO:1, which represents the nucleotide sequence encoding the CBF9 polypeptide. In other words, the reference sequence is no longer "SEQ ID NO:1, as a whole."

At page 22 of the Office Action mailed February 26, 2004, the Examiner states the following:

> Skolnick et al. [Citation] teaches that assigning functional activities for any particular protein or protein family based upon sequence homology alone is inaccurate; the fact that another nucleic acid molecule comprises a polynucleotide sequence that is similar to the polynucleotide sequence set forth in SEQ ID NO: 1 cannot be construed as evidence that the other nucleic acid molecule can be used as a biomarker to asses whether a patient is afflicted with colorectal cancer, since Skolnick et al. teaches, even in situations where there is some confidence of a similar overall structure between two proteins only experimental research can confirm the artisan's best guess as to the function of the structurally related protein; and it follows that any association of the expression of the other nucleic acid molecule and the presence of colorectal cancer can only be determined empirically.

The above citation indicates that the Examiner construes the teachings of Skolnick to indicate that function of a protein can not be reasonably be predicted based solely on sequence similarity. In the Response of August 17, 2004, Applicants submitted that if a protein having a known function and a variant of a protein are 90% identical, the skilled artisan can reliably predict and accurately predict the function of the variant. At page 7 of the Final Office Action, the Examiner was not persuaded, stating that "Applicant has not provided any factual evidence to support this assertion." Applicants provide herewith the factual evidence requested by the Examiner.

As an example of the inadequacy of sequence-based methods for predicting function, Skolnick cites one of his previous papers - Fetrow and Skolnick (1998) ("Fetrow"). Fetrow states the following:

> Unfortunately, current methods [for predicting function], including global sequence alignment and local sequence motif identification, are limited by the extent of sequence similarity between sequences of unknown and known function; these methods increasingly fail as the sequence identity diverges into and beyond the twilight zone of sequence identity.

See abstract. The above passage from Fetrow indicates that predicting function is only problematic once there is no longer a certain threshold of sequence similarity. It follows that Fetrow teaches that predicting function is successful if there is enough similarity between the two sequences. The passage from Fetrow indicates that the inadequacy of sequence-based functional prediction occurs within the "twilight zone of sequence identity" and beyond.

As evidence of the "twilight zone of sequence identity," Applicants submit herewith Rost B., "Twilight zone of protein sequence alignments" (1999)("Rost"). Rost discloses that the "twilight zone of sequence identity" is 20-35% pairwise sequence identity. *See* Abstract and page 91, right-hand column. Applicants note that this level of identity is far below the 90% level of identity required by claim 32, 50 and 57. Furthermore, Rost discloses that "[s]equence alignments unambiguously distinguish between protein pairs of similar and non-similar structure when the pairwise sequence identity is high (>40% for long alignments)." *See* Abstract.

The teachings of Skolnick can only be understood by also taking into account the teachings of Fetrow and Rost. Skolnick does not teach, therefore, that protein function predictions based on sequence similarity are inadequate in all cases. Instead, Skolnick teaches that there is only a problem in predicting function when there isn't enough similarity between two sequences (i.e., the "twilight zone" or beyond). This is made clear when Skolnick states "[a]lthough sequence-based approaches to protein-function have proved to be very useful, alternatives are needed to assign the biochemical function of the 30-50% pf proteins whose functions cannot be assigned by an current methods." *See* page 37, right-hand column. This indicates that sequence-based approaches are useful in certain cases, i.e., when there is a sufficient level of sequence identity. The teachings of Fetrow and Rost indicate that sequence-based approaches are useful in those cases where there is greater than 40% sequence identity between the known and unknown sequences. In view of claims 32, 50 and 57 requiring at least 90% sequence identity to the nucleotide sequence encoding the CBF9 polypeptide, Applicants respectfully request reconsideration and withdrawal of the rejection for lack of written description.

3. Objections

At section 12 of the Final Office Action, the Examiner objects to claims 32 and 50 for reciting "detecting the level of expression." The Examiner asserts that the level of expression can be measured, but not detected. Applicants respectfully traverse the objection. Claims 32 and

50 are amended to recite "measuring the level of a polynucleotide," as suggested by the Examiner. Accordingly, Applicants respectfully request withdrawal of the objection to claims 32 and 50.

At section 13 of the Final Office Action, the Examiner objects to claims 32 and 50 for reciting "indicative of cancer" where the claims are directed to a method of diagnosing "colorectal cancer." Applicants respectfully traverse the objection. Claims 32 and 50 are amended to recite "indicative of colorectal cancer" in conformity with the preamble. Accordingly, Applicants respectfully request withdrawal of the objection to claims 32 and 50.

At section 14 of the Final Office Action, the Examiner objects to claim 50 for reciting a step denoted as (a) without reciting an additional step. Applicants respectfully traverse the objection. Claim 50 is amended to cancel the reference to step (a). Accordingly, Applicants respectfully request withdrawal of the objection to claims 32 and 50.

4. 35 U.S.C. § 112, second paragraph

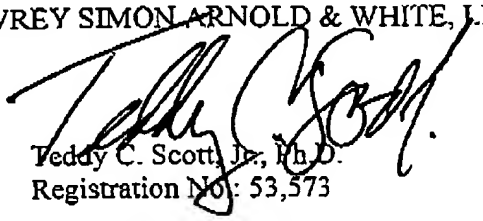
At section 15 of the Final Office Action, the Examiner rejects claims 57-59 under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner alleges that the claims do not recite a positive process step that clearly relates back to the purpose of the invention recited in the preamble of the claim. Applicants respectfully traverse the rejection. Claim 57 is amended to add a recitation that "an increase in the level of the expression product relative to normal colorectal tissue is indicative of colorectal cancer" in conformity with the preamble. Accordingly, Applicants respectfully request withdrawal of the objection to claim 32.

B. Conclusion

In view of the above amendments and remarks, Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY SIMON ARNOLD & WHITE, LLP

By: 

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